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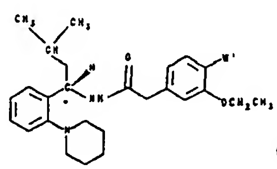
(54) Titre : ACIDE (S)(+)-2-ETHOXY-4-[N-[1-(2-PIPERIDINOPHENYL)-3-METHYL-1-BUTYL]AMINOCARBONYLMETHYL]BENZOIQUE
(54) Title: (S)(+)-2-ETHOXY-4-[N-[1-(2-PIPERIDINO-PHENYL)-3-METHYL-1-BUTYL]AMINOCARBONYLMETHYL]BENZOIC ACID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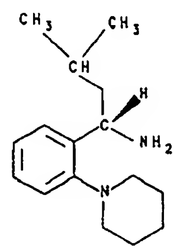
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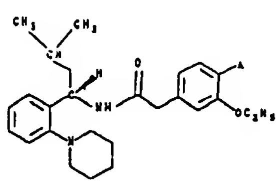
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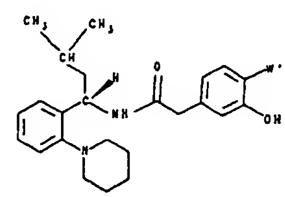
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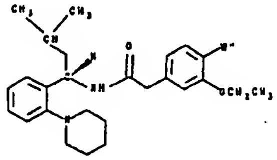

(VII)

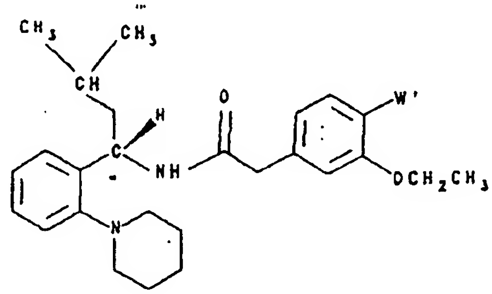
(57) Abrégé/Abstract:
The present application relates to the new (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoic acid and the salts thereof, which have valuable pharmacological properties, namely an effect on the intermediate metabolism, but particularly the effect of lowering blood sugar. The (S)-enantiomer has the general formula: (see formula VII) wherein W' represents a carboxy group or an alkoxycarbonyl group having a total of 2 to 5 carbon atoms, wherein the alkyl moiety of the alkoxy group may be substituted by a phenyl group. The invention also relates to the new

(57) Abrégé(suite)/Abstract(continued):
intermediate products of formulae I, III, IV, and VII and the addition salts thereof. The intermediates are compound of general formulae: (see formulas I, III, IV, and V) A represents a group which can be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis, W represents a carboxy group or an alkoxycarbonyl group having a total of 2 to 5 carbon atoms, wherein the alkyl moiety of the alkoxy group may be substituted by a phenyl group, and W' represents a group which may be converted by oxidation into a carboxy group, and the addition salts thereof. The new compounds can be produced using methods which are known for analogous compounds.

Abstract

The present application relates to the new (S) (+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoic acid and the salts thereof, which have valuable pharmacological properties, namely an effect on the intermediate metabolism, but particularly the effect of lowering blood sugar.

The (S)-enantiomer has the general formula:

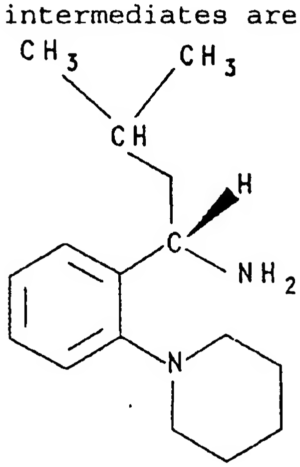


(VIII)

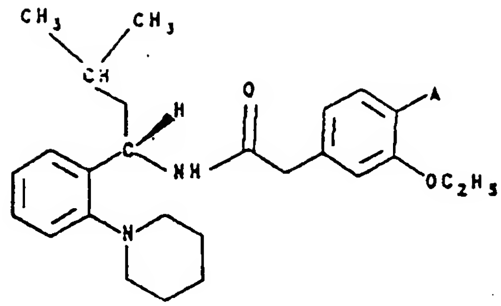
wherein

W′ represents a carboxy group or an alkoxycarbonyl group having a total of 2 to 5 carbon atoms, wherein the alkyl moiety of the alkoxy group may be substituted by a phenyl group.

The invention also relates to the new intermediate products of formulae I, III, IV, and VII and the addition salts thereof. The intermediates are compound of general formulae:



(I)



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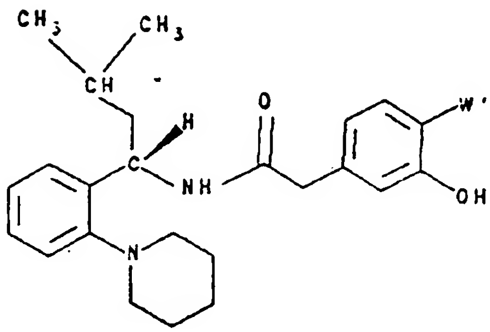

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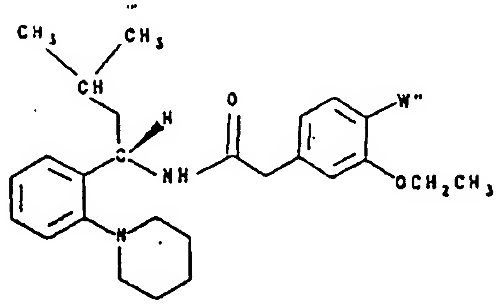


(VII)

A represents a group which can be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis,

W′ represents a carboxy group or an alkoxycarbonyl group having a total of 2 to 5 carbon atoms, wherein the alkyl

moiety of the alkoxy group may be substituted by a phenyl group, and

W″ represents a group which may be converted by oxidation into a carboxy group, and the addition salts thereof.

The new compounds can be produced using methods which are known for analogous compounds.

CLAIMS:

1. (S)(+)-2-Ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid or a physiologically acceptable salt thereof with an inorganic or organic acid or base, having an optical purity of at least ee = 95%.

2. Compound according to claim 1 having an optical purity of at least ee = 98%.

3. A physiologically acceptable salt of the compound according to claim 1 or 2 with an organic or inorganic acid or base.

4. A pharmaceutical composition containing a compound according to any one of claims 1 to 3 or a physiologically acceptable salt thereof, together with one or more inert carriers and/or diluents.

5. A pharmaceutical composition according to claim 4 which is in single dose form wherein the dose is in the range from 0.25 to 5.0 mg.

6. A pharmaceutical composition according to claim 5 wherein the single dose is 0.5 mg.

7. A pharmaceutical composition according to claim 5 wherein the single dose is 1.0 mg.

8. A pharmaceutical composition according to claim 5 wherein the single dose is 2.0 mg.

9. Use of the compound according to any one of claims 1 to 3 or a physiologically acceptable salt thereof for treating diabetes mellitus.

10. A process for preparing a pharmaceutical composition according to claim 4, characterised in that a compound according to any one of claims 1 to 3 or a physiologically acceptable salt thereof is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

11. A process according to claim 10, wherein the pharmaceutical composition is prepared in single dose form and the single dose is in the range from 0.25 to 5.0 mg.

12. A process according to claim 11, wherein the single dose is 0.5 mg.

13. A process according to claim 11 wherein the single dose is 1.0 mg.

14. A process according to claim 11 wherein the single dose is 2.0 mg.

15. Use of (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid as active substance, or of a physiologically acceptable salt thereof, in the preparation of a long-term antidiabetic agent, characterised in that, compared with double the single dose in the administration of a racemate, unnecessarily high and long-lasting substance loading is avoided, as a result of which substantially lower levels of active substance in the plasma are obtained which go beyond the normal advantage of halving the dose in the administration of enantiomers.

16. Use of (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid according to claim 15, characterised in that the active substance with an optical purity of at least ee = 95%, or a physiologically acceptable salt thereof, is used.

17. Use of (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid according to claim 15, characterised in that the active substance with an optical purity of at least ee = 98%, or a physiologically acceptable salt thereof, is used.

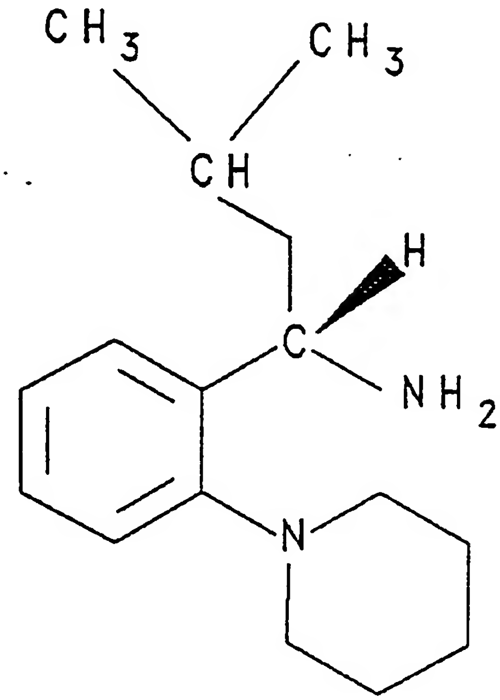
18. A pharmaceutical composition for oral administration to a warm blood animal or human for treating diabetes mellitus in long term therapy with the improvement that, compared with double the single dose in the administration of the corresponding racemate, unnecessarily high and long-lasting substance loading is avoided, as a result of which substantially lower levels of active substance in the plasma are obtained which go beyond the normal advantage of halving the dose for administration which composition comprises (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoic acid or a physiologically acceptable salt thereof, together with a suitable diluent or carrier.

19. A composition according to claim 18 wherein the (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid or physiologically acceptable salt thereof has an optical purity of at least ee = 95%.

20. A composition according to claim 18 wherein the (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid or physiologically acceptable salt thereof has an optical purity of at least ee = 98%.

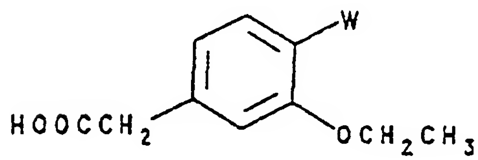
21. Process for preparing the compound according to any one of claims 1 to 3, characterised in that

a) the (S)-amine of formula



(I)

is reacted with a carboxylic acid of general formula

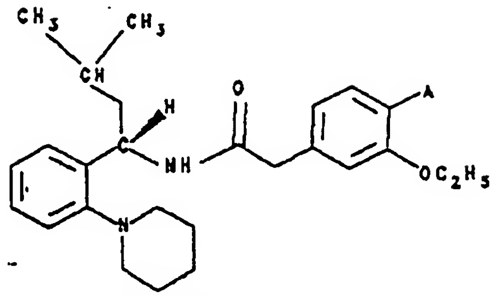


(II)

wherein
W represents a carboxy group or a carboxy group protected by a protecting group,

or with a reactive derivative thereof, optionally prepared in the reaction mixture, and subsequently, if necessary, any protecting group used is cleaved or

b) an (S)-compound of general formula

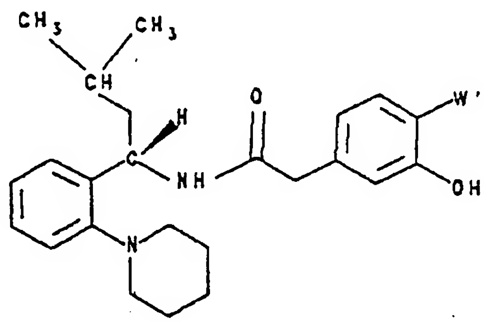


(III)

is cleaved by hydrolysis when A represents a functional derivative of the carboxy group,

by thermolysis when A represents a tert.butyloxycarbonyl group, or by hydrogenolysis when A represents a benzyloxycarbonyl group, or

c) an (S)-compound of general formula



(IV)

wherein
W' represents a carboxy group or an alkoxycarbonyl group having a total of 2 to 5 carbon atoms, wherein the alkyl moiety of the alkoxy group may be substituted by a phenyl group,

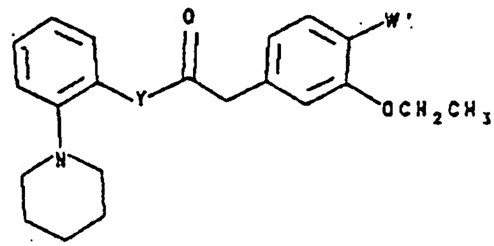
is reacted with a compound of general formula

$$Z - CH_2 - CH_3 \qquad (V)$$

wherein
Z represents a nucleophilically exchangeable group or,

together with the adjacent hydrogen atom, represents a diazo group, and subsequently, if necessary, a compound thus obtained is hydrolysed or hydrogenolysed or

d) a compound of general formula

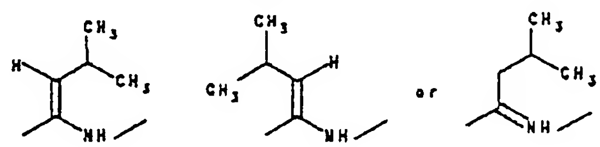


(VI)

wherein

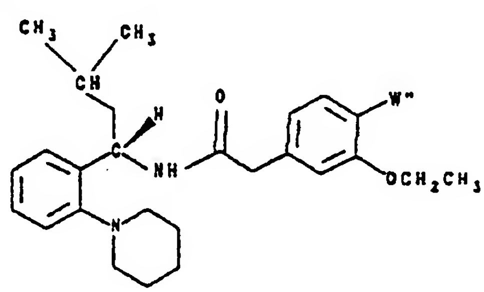
W' represents a carboxy group or an alkoxycarbonyl group having a total of 2 to 5 carbon atoms, wherein the alkyl moiety of the alkoxy group may be substituted by a phenyl group, and

Y represents a group of the formula



is enantioselectively reduced and subsequently, if necessary, a compound thus obtained is hydrolysed or

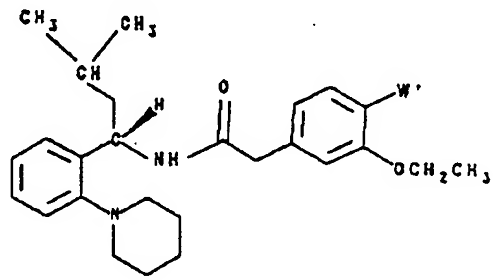
e) an (S)-compound of general formula



(VII)

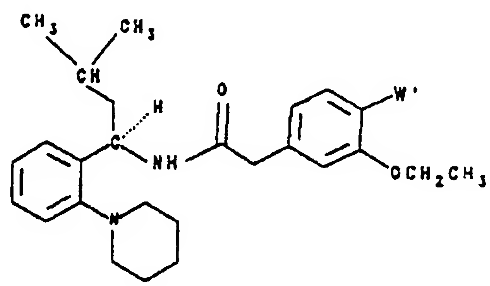
wherein
W" represents a group which can be converted into a carboxy group by oxidation is oxidised or

f) a mixture consisting of any desired amount of the (S)-enantiomer of general formula



(VIII)

and any desired amount of the (R)-enantiomer of general formula



(IX)

wherein
W' represents a carboxy group or an alkoxycarbonyl group having a total of 2 to 5 carbon atoms, wherein the alkyl moiety of the alkoxy group may be substituted by a phenyl group, is separated and

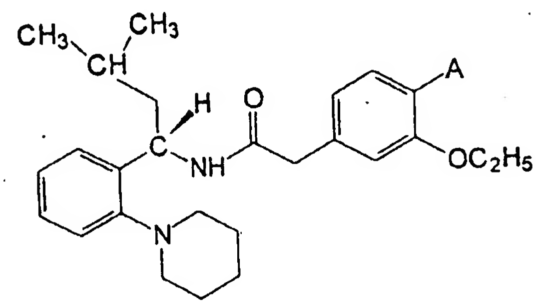
a compound thus obtained is, if necessary converted by recrystallisation into a compound with a higher enantiomeric purity, crystallisation from ethanol/water (2/1) producing the high melting form with a melting

point of 130-131°C and crystallisation from petroleum ether/toluene (5/3) producing the low-melting form with a melting point of 99-101°C, and

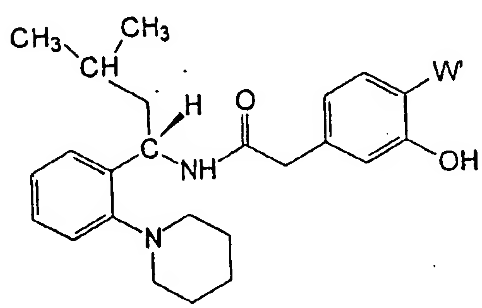
a compound thus obtained is converted into a physiologically acceptable salt thereof with an organic or inorganic acid or base.

22. (S)-3-Methyl-1-(2-piperidino-phenyl)-1-butylamine or an acid addition salt thereof.

23. A compound of general formula:

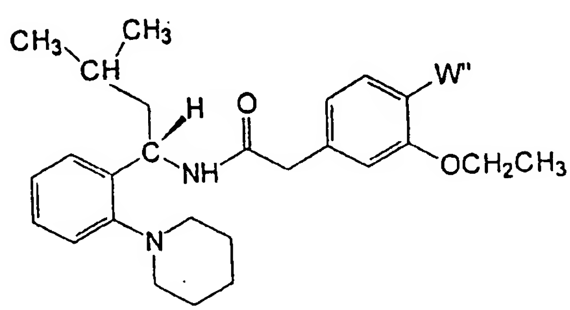


(III)



(IV)

or



(VII)

wherein

A represents an alkoxycarbonyl group having a total of 2 to 5 carbon atoms and wherein the alkyl moiety of the alkoxy group may be substituted by a phenyl group; an aminocarbonyl, cyano, amidino, tetrazolyl, 1,3-oxazol-2-yl or a 1,3-oxazolin-2-yl group,

W′ represents a carboxy group or an alkoxycarbonyl group having a total of 2 to 5 carbon atoms, wherein the alkyl moiety of the alkoxy group may be substituted by a phenyl group, and

W″ represents a group which may be converted by oxidation into a carboxy group, selected from the group consisting of a formyl group, an acetyl of a formyl group, a hydroxymethyl group, an ether of a hydroxymethyl group, a malonic acid-(1)-yl group and a malonic ester-(1)-yl group;

or an addition salt thereof.

24. A compound of formula (III) according to claim 23, or an addition salt thereof, wherein A is a tert.butyloxycarbonyl or a benzyloxycarbonyl group.

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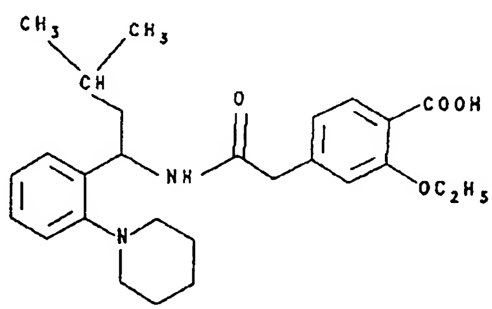
Case 5/1072-FL

(S)(+)-2-Ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid, pharmaceutical compositions containing this compound and processes for the preparation thereof

EP-B-0147850 describes inter alia the racemate of 2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoic acid (Code No.: AG-EE 388 ZW) of the formula



and EP-B-0207331 describes two other polymorphous forms of this compound. This compound and the physiologically acceptable salts thereof have valuable pharmacological properties, namely an effect on the intermediate metabolism, but more particularly the effect of lowering blood sugar.

The two enantiomers of this compound, namely (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoic acid (Code No.: AG-EE 623 ZW) and (R)(-)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]benzoic acid (Code No.: AG-EE 624 ZW) have been tested for their

blood sugar-lowering effect on female rats.

It was found, surprisingly, that the (S)-enantiomer (AG-EE 623 ZW) is the effective enantiomer and its effect lasts longer than 6 hours in the rat.

On the basis of these findings in the rat, it seems appropriate to use exclusively AG-EE 623 ZW in humans, thereby reducing the dose by 50%, compared with the dose of AG-EE 388 ZW. This and a relatively long period of activity have been found in humans. However, it was also found in the human studies that AG-EE 623 ZW has surprising pharmacokinetic properties which could not have been foreseen on the basis of the AG-EE 388 ZW data. AG-EE 623 ZW thus has surprising therapeutic advantages over the racemate AG-EE 388 ZW.

The surprising findings in humans are:

(a) The AG-EE 623 ZW levels fall more rapidly towards zero than the AG-EE 388 ZW levels, even when the dosage is absolutely the same, which could not be expected in view of the relatively long period of activity.
(b) In relation to the lowering of blood sugar achieved, substantially lower plasma levels of AG-EE 623 ZW occur than might have been expected by halving the dosage of AG-EE 388 ZW.
(c) The blood sugar lowering activity occurs more rapidly after the administration of AG-EE 623 ZW than after the administration of AG-EE 388 ZW.

The amazing difference between the two enantiomers is the fact that the effective enantiomer, AG-EE 623 ZW, in spite of having a relatively long period of activity, is surprisingly eliminated more rapidly than the ineffective enantiomer, AG-EE 624 ZW, as demonstrated by Figures 1 and 2. After the administration of the

racemate, the ineffective enantiomer, AG-EE 624 ZW, is therefore present not only as an unnecessary additive in plasma concentrations which are just as high as those of the effective enantiomer, AG-EE 623 ZW, but is present in unexpectedly higher maximum and long-lasting levels. The effect of this, e.g. on administration of a tablet containing 2 mg of AG-EE 388 ZW or one tablet containing 1 mg of AG-EE 623 ZW to 12 and 6 test subjects, respectively, is that the maximum concentrations are 84 ± 25 and 28 ± 18 ng/ml, respectively, and the concentrations after 4 hours are 19 ± 8 and 0.7 ± 1.0 ng/ml, respectively, after 5 hours 13 ± 6 and 0.3 ± 0.7 ng/ml, respectively, and after 6 hours 10 ± 6 and 0.3 ± 0.7 ng/ml, respectively.

The surprisingly quick onset of the lowering of blood sugar by AG-EE 623 ZW, compared with AG-EE 388 ZW, is particularly advantageous for diabetics, since the rapid onset results in optimum control of the disease.

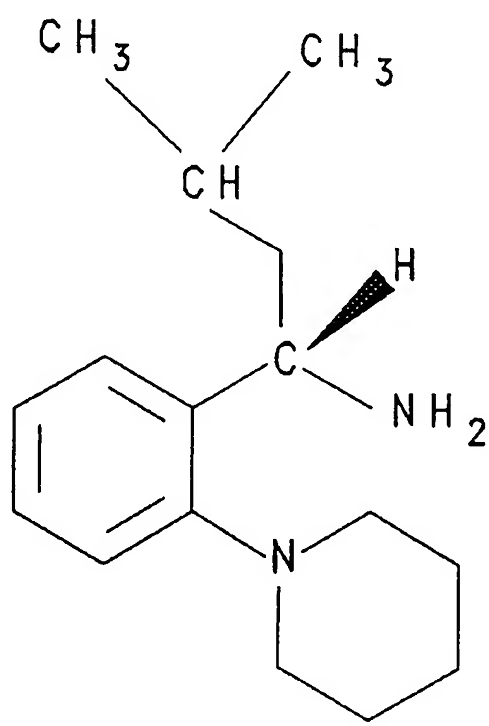
Thus, compared with the administration of AG-EE 388 ZW, the surprising advantage of the administration of AG-EE 623 ZW is that unnecessarily high and long-lasting levels of the substance in the body are avoided, which is of major importance in long term therapy, such as that of diabetic mellitus.

Human studies have shown that the new (S)-enantiomer, namely (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid, as a vehicle of blood sugar-lowering activity, is far superior to AG-EE 388 ZW, because of its surprisingly rapid elimination from the blood, which was not foreseeable in view of its relatively long duration of activity, and these superior qualities go far beyond the "normal" advantage of an enantiomer over its racemate, namely the advantage of halving the dose.

The present invention therefore relates to the new (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoic acid or an (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoic acid, which is substantially optically pure, e.g. having an optical purity of at least ee = 95%, preferably 98 to 100%, the physiologically acceptable salts thereof with inorganic or organic acids or bases, pharmaceutical compositions containing this compound or the physiologically acceptable salts thereof and processes for preparing them.

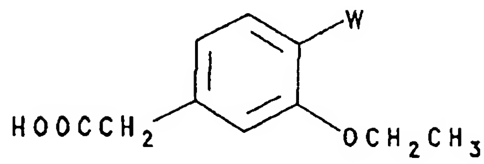
According to the invention, the new compound is obtained by the following methods:

a) reaction of the (S)-amine of formula



(I)

with a carboxylic acid of general formula



(II)

wherein
W represents a carboxy group or a carboxy group protected by a protecting group,

or with the reactive derivatives thereof optionally prepared in the reaction mixture and, if necessary, subsequent cleaving of a protecting group.

Reactive derivatives of a compound of general formula II may be, for example, the esters thereof such as the methyl, ethyl or benzyl ester, the thioesters thereof such as the methylthio or ethylthioesters, the halides thereof such as acid chloride, the anhydrides or imidazolides thereof.

The reaction is conveniently carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile or dimethylformamide, optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of ethylchloroformate, isobutylchloroformate, thionylchloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, or an agent which activates the amino group, e.g. phosphorus trichloride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as

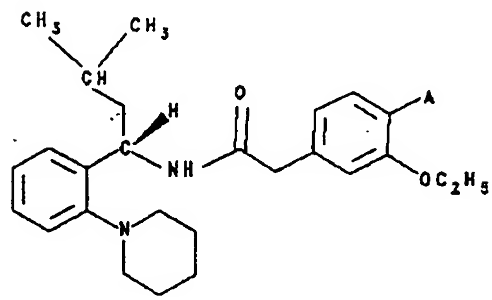
triethylamine or pyridine which may simultaneously serve as solvent, at temperatures between -25 and 250°C, but preferably at temperatures between -10°C and the boiling temperature of the solvent used. The reaction may also be carried out without a solvent and moreover any water formed during the reaction may be removed by azeotropic distillation, e.g. by heating with toluene using a water separator, or by the addition of a drying agent such as magnesium sulphate or molecular sieve.

If necessary, the subsequent cleaving of a protecting group is preferably carried out by hydrolysis, conveniently either in the presence of an acid such as hydrochloric, sulphuric, phosphoric, trifluoroacetic or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, methanol, methanol/water, ethanol, ethanol/water, water/isopropanol or water/dioxane at temperatures between -10 and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture.

A tert.-butyl group used as protective group may also be cleaved thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran, dioxane or glacial acetic acid and preferably in the presence of a strong acid such as trifluoroacetic, hydrobromic, p-toluenesulphonic, sulphuric, phosphoric or polyphosphoric acid.

Moreover, a benzyl group used as protective group may also be cleaved hydrogenolytically in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide.

b) Cleaving an (S)-compound of general formula



(III)

wherein
A represents a group which may be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis.

Examples of hydrolysable groups include functional derivatives of the carboxy group such as the unsubstituted or substituted amides, esters, thioesters, orthoesters, iminoethers, amidines or anhydrides thereof, a nitrile group, a tetrazolyl group, an optionally substituted 1,3-oxazol-2-yl or 1,3-oxazolin-2-yl group and

examples of thermolytically cleavable groups include the esters with tertiary alcohols, e.g. a tert.butylester, in which A represents a tert.butyloxycarbonyl group, and

examples of hydrogenolytically cleavable groups include the aralkyl groups, e.g. a benzyl group in which A represents a benzyloxycarbonyl group.
The hydrolysis is conveniently carried out either in the presence of an acid such as hydrochloric, sulphuric, phosphoric, trifluoroacetic or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol,

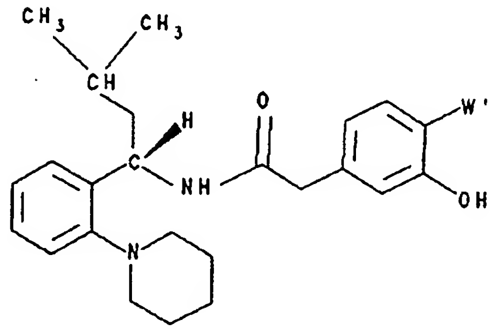
water/isopropanol or water/dioxane at temperatures between -10 and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture.

If A in a compound of general formula III represents a nitrile or aminocarbonyl group, these groups may be converted into the carboxy group by means of 100% phosphoric acid at temperatures between 100 and 180°C, preferably at temperatures between 120 and 160°C, or using a nitrite, e.g. sodium nitrite, in the presence of an acid such as sulphuric acid, whilst the latter may conveniently be used as solvent at the same time, at temperatures between 0 and 50°C.

If A in a compound of general formula III represents a tert.butyloxycarbonyl group, for example, the tert.butyl group may also be cleaved thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran, dioxane or glacial acetic acid and preferably in the presence of a strong acid such as trifluoroacetic acid, hydrobromic acid, p-toluenesulphonic acid, sulphuric acid, phosphoric acid or polyphosphoric acid, at temperatures between 0 and 100°C, preferably at temperatures between 20°C and the boiling temperature of the solvent used.

If A in a compound of general formula III represents a benzyloxycarbonyl group, for example, the benzyl group may also be cleaved hydrogenolytically in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, methanol/water, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide, preferably at temperatures between 0 and 50°C, e.g. at ambient temperature and under a hydrogen pressure of from 1 to 5 bar.

c) Reaction of an (S)-compound of general formula



(IV)

wherein
W' represents a carboxy group or an alkoxycarbonyl group having a total of 2 to 5 carbon atoms, wherein the alkyl moiety of the alkoxy group may be substituted by a phenyl group,

with a compound of general formula

$$Z - CH_2 - CH_3 \qquad (V)$$

wherein
Z represents a nucleophilically exchangeable group such as a halogen atom, a sulphonyloxy group or, together with the adjacent hydrogen atom, represents a diazo group, optionally followed by hydrolysis or hydrogenolysis.

The reaction is conveniently carried out with a corresponding halide, sulphonic acid ester or sulphuric acid diester, e.g. with ethyl bromide, ethyl iodide, diethylsulphate, ethyl p-toluenesulphonate or ethylmethanesulphonate, or with diazoethane, optionally in the presence of a base such as sodium hydride, potassium carbonate, sodium hydroxide, potassium tert.butoxide or triethylamine, preferably in a suitable solvent such as acetone, diethylether, tetrahydrofuran, dioxane,

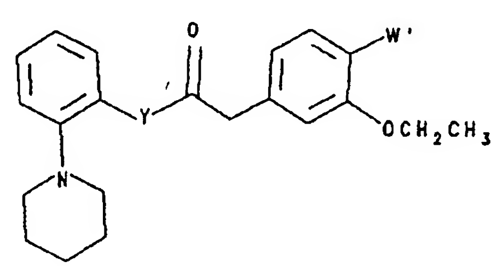
pyridine or dimethylformamide at temperatures between 0 and 100°C, preferably at temperatures between 20 and 50°C.

If W' in a compound of general formula IV represents a carboxy group, this can be converted into the corresponding ester compound.

If necessary, the subsequent hydrolysis is carried out either in the presence of an acid such as hydrochloric, sulphuric, phosphoric, trifluoroacetic or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, methanol, methanol/water, ethanol, ethanol/water, water/isopropanol or water/dioxane at temperatures between -10 and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture, or

the subsequent hydrogenolysis is carried out in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide under a hydrogen pressure of from 1 to 10 bar.

d) Enantioselective reduction of a compound of general formula



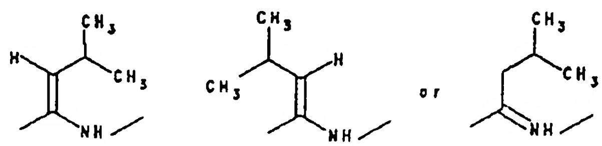
(VI)

wherein

W' represents a carboxy group or an alkoxycarbonyl group

having a total of 2 to 5 carbon atoms, wherein the alkyl moiety of the alkoxy group may be substituted by a phenyl group, and

Y represents a group of the formula



and optional subsequent hydrolysis.

The reduction is preferably carried out with hydrogen in the presence of a suitable chiral hydrogenation catalyst in a suitable solvent such as methanol, ethanol, isopropanol, ethyl acetate, dioxane, tetrahydrofuran, methanol/tetrahydrofuran, methanol/methylene chloride, ethanol/methylene chloride of isopropanol/methylene chloride at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 50°C, under a hydrogen pressure of between 1 and 1000 bar, preferably between 5 and 100 bar, and conveniently with the addition of 0.1 to 5%, preferably 0.3 to 1%, of titanium(IV)tetraisopropoxide, preferably with the exclusion of oxygen from the air. The reduction is preferably carried out with the (Z)-form of a compound of general formula VI.

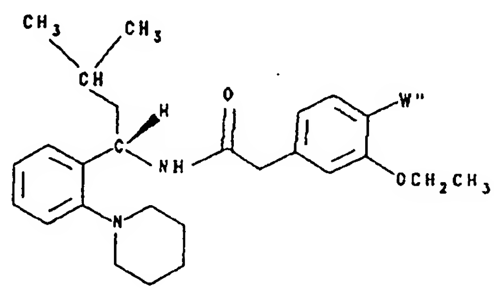
Examples of chiral hydrogenation catalysts are the corresponding metal ligand complexes such as Ru(OCO-CH_3)$_2$[(S)-BINAP], Ru_2Cl_4[(S)-BINAP]$_2$ x $N(C_2H_5)_3$, Rh[(S)-BINAP-NBD]ClO_4 or Rh[(-)-NORPHOS-COD]BF_4.

During the catalytic hydrogenation, a benzyloxycarbonyl group may simultaneously be reduced and converted into

the carboxy group.

If necessary, the subsequent hydrolysis is carried out either in the presence of an acid such as hydrochloric, sulphuric, phosphoric, trifluoroacetic or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, methanol, methanol/water, ethanol, ethanol/water, water/isopropanol or water/dioxane at temperatures between -10 and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture.

e) Oxidation of an (S)-compound of general formula



(VII)

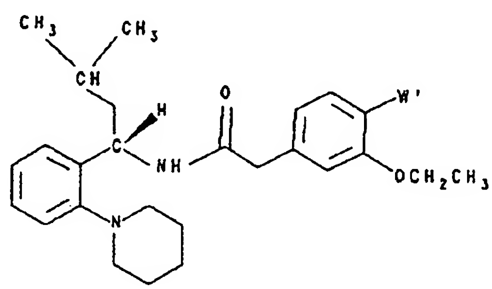
wherein
W" represents a group which may be converted into a carboxy group by oxidation.

An example of an oxidisable group of this kind might be a formyl group and the acetals thereof, a hydroxymethyl group and the ethers thereof, an unsubstituted or substituted acyl group such as acetyl, chloroacetyl, propionyl, malonic acid-(1)-yl group or a malonic ester-(1)-yl group.

The reaction is carried out with an oxidising agent in a suitable solvent such as water, glacial acetic acid,

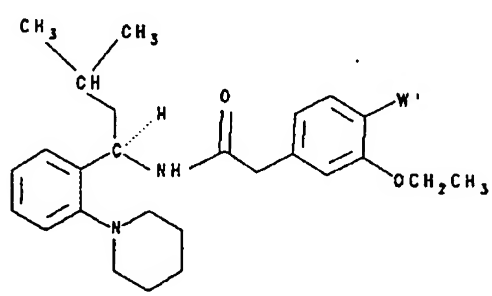
methylene chloride, dioxane or glycoldimethylether at temperatures between 0 and 100°C, but expediently at temperatures between 20°C and 50°C. However, the reaction is preferably carried out with silver oxide/sodium hydroxide solution, manganese dioxide/acetone or methylene chloride, hydrogen peroxide/sodium hydroxide solution, bromine or chlorine/sodium or potassium hydroxide solution, chromium trioxide/pyridine or pyridinium chlorochromate.

f) Separation of a mixture, consisting of any desired amount of the (S)-enantiomer of general formula



(VIII)

and any desired amount of the (R)-enantiomer of general formula



(IX)

wherein

W' represents a carboxy group or an alkoxycarbonyl group having a total of 2 to 5 carbon atoms, wherein the alkyl

moiety of the alkoxy group may be substituted by a phenyl group,

preferably a 50/50 mixture, via the diastereomeric adducts, complexes or salts thereof, and followed if necessary by hydrolysis or hydrogenolysis.

The separation is preferably carried out using column or HPL chromatography by forming the diastereomeric adducts or complexes on a chiral phase.

If necessary, the subsequent hydrolysis is carried out either in the presence of an acid such as hydrochloric, sulphuric, phosphoric, trifluoroacetic or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, methanol, methanol/water, ethanol, ethanol/water, water/isopropanol or water/dioxane at temperatures between -10 and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture, or

the subsequent hydrogenolysis is carried out in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide under a hydrogen pressure of from 1 to 10 bar.

The (S)-enantiomer thus obtained according to the invention, having an optical purity of, preferably, at least 90% can be converted by fractional crystallisation into an (S)-enantiomer having an optical purity of at least 95%, preferably 98 to 100%.

The same applies to the (S)-compounds according to the invention of formulae III, IV and VII, and more

particularly the esters thereof.

The (S)-enantiomer thus obtained according to the invention can be converted into the salts thereof, more particularly, for pharmaceutical use, into the physiologically acceptable salts thereof with inorganic or organic acids or bases. Examples of such acids include hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, lactic acid, citric acid, tartaric acid, succinic acid, maleic acid or fumaric acid and examples of bases include sodium hydroxide, potassium hydroxide, calcium hydroxide, cyclohexylamine, ethanolamine, diethanolamine, triethanolamine, ethylenediamine or lysine.

The compounds of formulae I to IX used as starting materials are known from the literature in some cases or may be obtained by methods known *per se*.

The (S)-amine of formula I can be obtained from the corresponding racemic amine

by racemate cleaving, e.g. by means of fractional crystallisation of the diastereomeric salts with suitable optically active acids, preferably with N-acetyl-L-glutamic acid, and if necessary recrystallisation and subsequent decomposition of the salts,

by column or HPL-chromatography on chiral phases, optionally in the form of an acyl derivative,

or by forming diastereomeric compounds, then separating and subsequently cleaving them.

Moreover, the (S)-amine of formula I may be prepared

by enantioselective reduction using hydrogen in the presence of a suitable chiral hydrogenation catalyst, starting from a corresponding N-acyl-ketimine or enamide, conveniently with the addition of 0.1 to 5% titanium tetraisopropoxide, optionally with subsequent cleaving of the acyl group such as the formyl or acetyl group,

by diastereoselective reduction of a corresponding ketimine or hydrazine chirally substituted at the nitrogen atom, using hydrogen in the presence of a suitable hydrogenation catalyst, expediently with the addition of 0.1 to 5% titanium tetraisopropoxide, and optionally followed by cleaving of the chiral auxiliary group, e.g. the (S)-1-phenethyl group, by catalytic hydrogenolysis, or

by diastereoselective addition of a corresponding organometallic compound, preferably a Grignard or lithium compound, to a corresponding aldimine chirally substituted at the nitrogen atom, optionally with the addition of 0.1 to 10% titanium tetraisopropoxide, subsequent hydrolysis and optional separation of the resulting diastereomers and subsequent cleaving of the chiral auxiliary group, e.g. the (R)-1-phenethyl group by catalytic hydrogenolysis,

and if necessary the (S)-amine may be obtained in a higher enantiomeric purity by salt formation with suitable optically active acids, preferably with N-acetyl-L-glutamic acid, and if necessary single or multiple recrystallisation and subsequent decomposition of the salt.

The compounds of general formulae III, IV and VII used as starting materials are obtained by reacting the (S)-amine I with a corresponding carboxylic acid or a

reactive derivative thereof and optionally subsequently splitting off any protecting group used.

The compound of general formula VI used as starting material is obtained by acylating the corresponding imino compound or the organometallic complexes thereof with the corresponding carboxylic acid or with the reactive derivatives thereof with optional subsequent cleaving of an ester group.

The new (S)-enantiomer is virtually non-toxic; for example, after a single administration of 1000 mg/kg p.o. (suspension in 1% methylcellulose) to 5 male and 5 female rats, no animals died within the observation period of 14 days.

In view of its pharmacological and pharmacokinetic properties, the (S)-enantiomer prepared according to the invention (AG-EE 623 ZW) and the physiologically acceptable salts thereof are suitable for the treatment of diabetes mellitus. For this purpose, AG-EE 623 ZW or the physiologically acceptable salts thereof, optionally combined with other active substances, may be incorporated in the conventional galenic preparations such as plain or coated tablets, capsules, powders, suppositories, suspensions or injectable solutions. The single dose for adults is 0.1 to 20 mg, preferably 0.25 to 5 mg, especially 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 or 5.0 mg, once, twice or three times a day.

The present invention further relates to the new (S)-amine of formula I which is a valuable intermediate product for preparing the new (S)-enantiomer, and the addition salts thereof with inorganic or organic acids.

The present invention also relates to the new compounds of general formulae III, IV and VII which are valuable

intermediate products for preparing the new (S)-enantiomer, and the addition salts thereof with inorganic or organic acids.

The Examples which follow are intended to illustrate the invention:

Example A

(S)-1-(2-Piperidino-phenyl)-3-methyl-1-butylamine

A stirred solution of 122 g (0.495 mol) of racemic 1-(2-piperidino-phenyl)-3-methyl-1-butylamine in 1000 ml of acetone is mixed with 93.7 g (0.495 mol) of N-acetyl-L-glutaminic acid. The mixture is refluxed over a vapour bath and methanol is added in batches (a total of about 80 ml) until a clear solution is obtained. After this has been left to cool and stand overnight at ambient temperature, the crystals obtained are removed by suction filtering, washed twice with 200 ml of cold acetone at -15°C and then dried. The product obtained [98.9 g; melting point: 163-166°C; $[\alpha]_D^{20} = + 0.286°$ (c = 1 in methanol)] is recrystallised from 1000 ml of acetone with the addition of 200 ml of methanol, thereby obtaining the (S)-1-(2-piperidino-phenyl)-3-methyl-1-butylamine as the addition salt of N-acetyl-L-glutaminic acid.

Yield: 65.1 g (60.4% of theory),
Melting point: 168-171°C

Calculated:	C 63.42	H 8.56	N 9.65
Found:	63.64	8.86	9.60

$[\alpha]_D^{20} = + 0.357°$ (c = 1 in methanol)

The free amine is obtained as an oil by liberation, for example, with a sodium hydroxide or ammonia solution, extraction with toluene, ether, ethylacetate or methylene chloride, for example, and drying, filtering and evaporation of the extract _in vacuo_.

The (S)-configuration of the amine was demonstrated as follows:

Reaction of the amine with (S')-1-phenethylisocyanate in ether to obtain the corresponding urea derivative [melting point: 183-184°C; $[\alpha]_D^{20} = -2.25°$ (c = 1 in methanol)], growing crystals from ethanol/water (8/1) and subsequent X-ray structural analysis showed the (S,S')-configuration for the urea derivative and consequently the (S)-configuration for the amine used.

<u>Enantiomeric purity</u> was determined as follows:

1. Acetylation of a sample of the amine with 1.3 equivalents of acetic anhydride in glacial acetic acid at 20°C overnight.
2. Investigation of the N-acetyl derivative (melting point: 128-132°C) by HPLC on a chiral phase HPLC column made by Baker, in which (S)-N-(3,5-dinitrobenzoyl)-2-phenyl-glycine is covalently bonded to aminopropyl silica gel (particle size 5 μm, spherical, pore size 60 A; column length: 250 mm with internal diameter 4.6 mm; eluant: n-hexane/isopropanol (100/5); flow rate: 2 ml/minute; temperature: 20°C; UV-detection at 254 nm.)

Found: peak 1(R): peak 2(S) = 0.75%: 99.25%,
ee (enantiomeric excess) = 98.5% (S).

The (S)-amine may be converted into the dihydrochloride hydrate thereof using ethereal hydrogen chloride solution.

Melting point: 135-145°C (decomposition)

Calc. (x H_2O):	C	56.99	H	8.97	N	8.31	Cl	21.02
Found:		56.85		8.93		8.38		21.25

$[\alpha]_D^{20} = +26.1°$ (c = 1 in methanol)

<u>Example B</u>

N-Acetyl-N-[1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl]-amine

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At ambient temperature, 4.7 ml (81.8 mMol) of glacial

acetic acid, 25.7 g (98.2 mMol) of triphenylphosphine, 34.2 ml (245 mMol) of triethylamine and 7.9 ml (81.8 mMol) of carbon tetrachloride are added to a solution of 20 g (81.8 mMol) of freshly prepared isobutyl-(2-piperidino-phenyl)-ketimine in 200 ml of acetonitrile and the resulting mixture is stirred for 18 hours at ambient temperature. It is then evaporated down *in vacuo* and distributed between ethyl acetate and water. The organic extract is dried and filtered and evaporated down *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 10/1), eluting first the (E)-form and then the (Z)-form.

(E)-form:
Yield: 6.1 g (26% of theory),
Melting point: 135-137°C (ethylacetate/petroleum ether)

Calculated:	C 75.48	H 9.15	N 9.78
Found:	75.47	9.35	9.70

(Z)-form:
Yield: 3.1 g (13% of theory),
Melting point: 140-143°C (ethylacetate)

Calculated:	C 75.48	H 9.15	N 9.78
Found:	75.56	9.30	9.79

Example C

N-Acetyl-N-[1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl]-amine

17 ml (0.18 mol) of acetic anhydride are added dropwise, at an internal temperature of 0°C, to a stirred solution of 44 g (0.18 mol) of freshly prepared isobutyl-(2-piperidino-phenyl)-ketimine in 440 ml of toluene. The mixture is stirred for a further 3 hours at 0°C and for 15 hours at ambient temperature, then evaporated down *in*

vacuo, the evaporation residue is dissolved in ethyl acetate and extracted several times with aqueous sodium hydrogen carbonate solution. The organic phase is dried, filtered and evaporated down in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 5/1), eluting first the (E)-form and then the (Z)-form.

(E)-form:

Yield: 3.0 g (5.8% of theory),

(Z)-form:

Yield: 17.8 g (34.5% of theory),

Melting point: 139-141°C (ethyl acetate)

Calculated:	C 75.48	H 9.15	N 9.78
Found:	75.68	8.99	9.86

Example D

N-Acetyl-N-[(S)-1-(2-piperidino-phenyl)-3-methyl-1-butyl]-amine

0.57 g (1.99 mMol) of (Z)-N-acetyl-N-[1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl]-amine, melting point 139-141°C, are dissolved in 10 ml of degassed solvent mixture (methanol/methylene chloride = 5/1) under an Argon atmosphere and added to a solution of 16.8 mg (1 mol %) of the NOYORI*-catalyst $Ru(O\text{-acetyl})_2[(S)\text{-BINAP}]$ (prepared from $[Ru(COD)Cl_2]_n$ with (S)-BINAP [= (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl], triethylamine and sodium acetate), and 3.4 mg (0.5 mol %) of titanium tetraisopropoxide in 10 ml of degassed solvent mixture (methanol/methylene chloride = 5/1). The reaction mixture is drawn into an autoclave which is evacuated at 10^{-2} mbar. It is rinsed several times with hydrogen at 4 bar and the mixture is then hydrogenated at 30°C under 100 bar until the hydrogen uptake has ceased (170 hours). Then the reddish-brown solution is evaporated

*Trade-mark

down *in vacuo*, the evaporation residue is refluxed with 30 ml of n-hexane and filtered hot to remove any insoluble matter. When the filtrate cools, crystallisation occurs.
Yield: 0.31 g (54% of theory),
Melting point: 127-131°C
enantiomeric purity: ee = 82% (S) [HPLC method: see Example A].
14% of the racemic N-acetyl-amine of melting point 154-156°C can be obtained from the insoluble matter obtained when boiling with 30 ml of n-hexane, by further decoction with n-hexane, filtration and crystallisation from the hexane solution.

Example E

(S)-1-(2-Piperidino-phenyl)-3-methyl-1-butylamine

1 g (3.47 mMol) of N-acetyl-N-[(S)-1-(2-piperidino-phenyl)-3-methyl-1-butyl]-amine (melting point: 128-133°C; ee = 99.4%] are refluxed in 10 ml of concentrated hydrochloric acid for 5.5 hours, then cooled and poured into a mixture of concentrated ammonia and ice. The mixture is extracted twice with ethyl acetate, the organic phase is washed with water, dried and filtered and then evaporated down *in vacuo*.
Yield: 0.84 g (98.8% of theory) oily amine.

By re-acetylation with 0.42 ml (1.3 equivalents) of acetic anhydride in 8.4 ml of glacial acetic acid overnight at ambient temperature, evaporation *in vacuo*, distribution of the evaporation residue between ethyl acetate and saturated aqueous sodium bicarbonate solution then drying, filtering and evaporation of the organic extract *in vacuo*, 0.83 g (84.7% of theory) of N-acetyl-N-[(S)-1-(2-piperidino-phenyl)-3-methyl-1-butyl]-amine are obtained (melting point: 130-132°C;

ee = 99.4%).

Example F

Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl)-aminocarbonylmethyl]-benzoate

Prepared from isobutyl-(2-piperidino-phenyl)-ketimine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid analogously to Example B. Purification by column chromatography on silica gel (toluene/acetone = 10/1), eluting first the (E)-form and then the (Z)-form.

(E)-form:
Yield: 4% of theory,
Melting point: 101-103°C

Calculated:	C 72.77	H 8.00	N 5.85
Found:	72.74	7.78	5.86

(Z)-form:
Yield: 28.1% of theory,
Melting point: 124-127°C (petroleum ether/toluene = 5/1)

Calculated:	C 72.77	H 8.00	N 5.85
Found:	72.90	7.86	5.83

Example G

N-[(S')-1-phenethyl]-N-[(S)-1-(2-piperidino-phenyl)-3-methyl-1-butyl]-amine

17 g (49 mMol) of N-[(S')-1-phenethyl]-isobutyl-(2-piperidino-phenyl)-ketimine, boiling point 150-155°C/0.3 torr [prepared from isobutyl-(2-piperidino-phenyl)-ketone and (S')-1-phenethyl-amine (made by Fluka, ee = 99.6%) in toluene + triethylamine by dropwise addition of a solution of titanium

tetrachloride in toluene] are dissolved in 170 ml of anhydrous ethanol. 1.7 g of titanium tetraisopropoxide and 8 g of Raney*nickel are added and the mixture is hydrogenated at 50°C under 200 bar of hydrogen. After 20 hours a further 8 g of Raney*nickel are added and the mixture is hydrogenated for a further 52 hours under the same conditions. The catalyst is filtered off over a layer of Celite*on a G3-mess and the filtrate is evaporated down in vacuo.

Yield: 13.1 g (76.6% of theory),

Boiling point: 152°C/0.2 torr

Calculated:	C 82.23	H 9.78	N 7.99
Found:	82.00	10.03	7.74

$[\alpha]_D^{20}$ = - 55.3° (c = 1.1 in methanol)

The diastereomeric purity is determined by HPLC on a Lichrosorb RP18* HPLC column made by E. Merck (Germany); column length: 250 mm with an internal diameter of 4 mm; particle size: 7 µm. Eluant: methanol/dioxane/0.1% aqueous sodium acetate solution, adjusted to pH 4.05 with acetic acid (135/60/5); temperature: 23°C; UV-detection at 254 nm.

Found: peak 1(S,S'): peak 2(R,S') = 98.4%: 1.4%,
de (diastereomeric excess) = 97.0% (S,S').

Example H

(S)-1-(2-Piperidino-phenyl)-3-methyl-1-butylamine

12.5 g (36 mMol) of N-[(S')-1-phenethyl]-N-[(S)-1-(2-piperidino-phenyl)-3-methyl-1-butyl]-amine with a de of 97.0% (S,S') are dissolved in 125 ml of water and 3.6 ml of conc. hydrochloric acid. 1.3 g of (10%) palladium/charcoal are added and the mixture is hydrogenated at 50°C under 5 bar of hydrogen. After the hydrogen uptake has ended (10 hours) the mixture is filtered over a layer of Celite* to remove the catalyst.

*Trade-mark

The filtrate is made alkaline with conc. ammonia with the addition of ice and extracted with ethyl acetate. The organic extract is dried and filtered and evaporated down *in vacuo*.

Yield: 6.4 g (72.1% of theory),

Boiling point: 115-117°C/0.4 torr

Enantiomeric purity: ee = 93.5% (S) [HPLC method (after previous acetylation): see Example A].

Example I

N-[(R')-1-phenethyl]-N-[(S)-1-(2-piperidino-phenyl)-3-methyl-1-butyl]-amine

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A solution of 2 g (6.84 mMol) of N-[(R')-1-phenethyl]-(2-piperidino-benzaldimine) [prepared from equimolar amounts of 2-piperidino-benzaldehyde and (R')-1-phenethylamine by standing overnight at ambient temperature and subsequent drying with sodium sulphate in ether solution] in 20 ml of anhydrous tetrahydrofuran is added dropwise to a solution of 27.4 mMol (4 equivalents) of isobutyl-magnesium bromide in 22 ml of anhydrous tetrahydrofuran, which is stirred in a bath at 60°C. After 18 hours the bath temperature is increased to 80°C and a further 2 equivalents of isobutyl-magnesium bromide in 11 ml of tetrahydrofuran are added. After 12 hours stirring at 80°C 2 equivalents of isobutyl-magnesium bromide solution are added once again. After about 90 hours at 80°C the mixture is cooled, excess conc. hydrochloric acid is added and the resulting mixture is evaporated to dryness in a water jet vacuum. The evaporation residue is dissolved in water and made alkaline with conc. ammonia. It is extracted with ether, the organic extract is dried over sodium sulphate, filtered and evaporated *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 95/5).

Yield: 0.20 g (8.3% of theory),
Melting point: < 20°C
The diastereomeric purity is determined by HPLC as in Example G.
Found: peak 1(R,R'): peak 2(S,R') = 4.4%:95.6%,
de (diastereomeric excess) = 91.2% (S,R').

In an analogous mixture with 2.0 g of the Schiff's base and a total of 6 equivalents of isobutyl-magnesium bromide in toluene/tetrahydrofuran (4/1) and with the addition of 5% titanium(IV)-tetraisopropoxide and heating for 60 hours at 100°C in a glass tank, a yield of 5% was achieved with a de of 97.6% (S,R').

Example K

(S)-1-(2-Piperidino-phenyl)-3-methyl-1-butylamine

A solution of 0.15 g (0.428 mMol) of N-[(R')-1-phenethyl]-N-[(S)-1-(2-piperidino-phenyl)-3-methyl-1-butyl]-amide (de = 91.2%), 0.47 ml (0.47 mMol) of 1N-hydrochloric acid and 1.5 ml of water is hydrogenated in the presence of 20 mg of 10% palladium/charcoal for 5 hours at 50°C under 3.4 bar of hydrogen. The mixture is filtered over kieselguhr, made alkaline with conc. ammonia and extracted with ethyl acetate. The extract is dried, filtered and evaporated in vacuo.
Yield: 0.066 g (62.8% of theory),
Melting point: < 20°C
Enantiomeric purity: ee = 87.6% (S) [HPLC method (after previous acetylation): see Example A].

Example 1

Ethyl (S)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate

0.48 g (1.91 mMol) of 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid, 0.60 g (2.29 mMol) of triphenyl-phosphine, 0.80 ml (5.73 mMol) of triethylamine and 0.18 ml (1.91 mMol) of carbon tetrachloride are added successively to a solution of 0.47 g (1.91 mMol) of (S)-3-methyl-1-(2-piperidino-phenyl)-1-butylamine (ee = 98.5%) in 5 ml of anhydrous acetonitrile and the resulting mixture is stirred for 20 hours at ambient temperature. It is then evaporated down *in vacuo* and distributed between ethyl acetate and water. The organic extract is dried and filtered and evaporated down *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 10/1).

Yield: 0.71 g (77.3% of theory),

Melting point: 110-112°C

Calculated:	C 72.47	H 8.39	N 5.83
Found:	72.29	8.42	5.80

The enantiomeric purity is determined by HPLC on a chiral phase HPLC column made by Baker, in which (S)-N-3,5-dinitrobenzoyl-leucine is covalently bound to aminopropyl silica gel (particle size: 5 μm, spherical, 60 A pore size; column length: 250 mm with an internal diameter of 4.6 mm; eluant: n-hexane/tetrahydro-furan/methylene chloride/ethanol (90/10/1/1); flow rate: 2 ml per minute; temperature: 20°C; UV detection at 242 nm).

Found: peak 1(R): peak 2(S) = 0.75%: 99.25%,
ee = 98.5% (S).

Example 2

Ethyl (S)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate

2.77 g (11 mMol) of 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid are added at ambient temperature to a solution of 2.71 g (11 mMol) of anhydrous (S)-3-methyl-1-(2-piperidino-phenyl)-1-butylamine (ee = 98.5%) in 30 ml of absolute toluene and the mixture is stirred until dissolved. Then 2.38 g (11.55 mMol) of N,N'-dicyclohexyl-carbodiimide are added and the mixture is stirred at ambient temperature. After 24 hours a further 0.54 g (2.14 mMol) of 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid and 0.48 g (2.33 mMol) of N,N'-dicyclohexylcarbodiimide are added and the mixture is stirred overnight. It is then cooled to an internal temperature of +5°C and suction filtered to separate the precipitate, which is washed once with 5 ml of toluene. The combined toluene filtrates are evaporated down *in vacuo* to a volume of about 10 ml. The resulting solution is heated over the steam bath and petroleum ether is added in batches thereto (total of 55 ml) until the turbidity remains. It is cooled in ice, whereupon crystallisation takes place. It is suction filtered and dried at 75°C/4 torr. The product obtained (4.57 g; melting point 111-112°C; ee = 98.9%) is suspended in 50 ml of petroleum ether. The mixture is heated over the steam bath and sufficient toluene is added in batches (8 ml in total) until a solution is obtained. This is then cooled in ice and suction filtered to separate the crystals, which are dried at 75°C/4 torr.

Yield: 3.93 g (74.3% of theory),

Melting point: 117-118°C

Calculated:	C 72.47	H 8.39	N 5.83
Found:	72.44	8.43	5.93

$[\alpha]_D^{20} = +9.4°$ (c = 1.01 in methanol)

Enantiomeric purity: ee = 99.9% [HPLC method: see Example 1]

Example 3

(S)-2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid

A solution of 3.79 g (7.88 mMol) of ethyl (S)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate (ee = 99.9%) in 37 ml of ethanol is stirred in a bath at 60°C and 10 ml (10 mMol) of 1N sodium hydroxide solution are added. After 4 hours stirring at 60°C, 10 ml (10 mMol) of 1N-hydrochloric acid are added in the warm and the mixture is left to cool to ambient temperature. After inoculation and standing overnight, the mixture is cooled for a further hour in ice, with stirring. The crystals are separated by suction filtering and washed twice with 5 ml of water. They are then dried at 75°C up to a final temperature of 100°C/4 torr in a vacuum drying cupboard over phosphorus pentoxide.
Yield: 3.13 g (87.7% of theory),
Melting point: 130-131°C (high-melting form)

Calculated:	C 71.64	H 8.02	N 6.19
Found:	71.48	7.87	6.39

$[\alpha]_D^{20} = + 7.45°$ (c = 1.06 in methanol)

The enantiomeric purity is determined by HPLC on a chiral phase HPLC column made by ChromTech* (Sweden) with an AGP(α1-acid glycoprotein) phase; internal diameter: 4.0 mm; length: 100 mm; particle diameter: 5 μm. Temperature: 20°C; eluant: 0.1% aqueous KH_2PO_4 solution (=A) + 20% acetonitrile (=B), gradient increase within 4 minutes to 40% (B); flow rate: 1 ml per minute; UV detection at 240 nm. Retention time (S)-enantiomer: 2.7 minutes; retention time (R)-enantiomer: 4.1 minutes.
*Trade-mark

Found: (S):(R) = 99.85%: 0.15%,
ee = 99.7% (S).

When a sample is recrystallised from ethanol/water (2/1) the melting point does not change. When a sample is heated in petroleum ether/toluene (5/3) the undissolved portion is filtered (melting point: 130-131°C) and the filtrate is rapidly cooled, the low melting form of the title compound is obtained, melting point 99-101°C.

Calculated:	C 71.64	H 8.02	N 6.19
Found:	71.66	7.97	6.44

The low melting form and the high melting form differ in their infra-red KBr spectra but not in their infra-red solution spectra (methylene chloride).

If a sample of the low melting form is heated beyond its melting point a second melting point is observed at 127-130°C.

If a sample of the low-melting form is recrystallised from ethanol/water (2/1), the high melting form is obtained.

The high melting form and the low melting form were investigated by Differential Scanning Calorimetry (DSC) [Mettler apparatus, TA-300 system; measuring cell: DSC 20; made by Mettler, CH-8306 Greifensee, Switzerland] with the following results:

Compound of Example 3	Heating rate 10°K/min.	Heating rate 3°K/min.
High melting form	Uniform melting peak with melting temperature of 133°C; melting enthalpy: 100 J/g	Uniform melting peak with melting tempera- of 132°C; melting enthalpy: 99.1 J/g
Low melting form	1st peak at 57°C (very weak) 2nd peak at 78°C (weak) 3rd endothermic peak at 107°C; melting enthalpy: 55 J/g 4th endothermic peak at 132°C melting enthalpy: 25 J/g	1st peak at 54°C (very weak; endothermic) 2nd endothermic peak at 104°C. melting temperature 102°C, melting enthalpy 52 J/g 3rd exothermic path of the base line by crystallisation of the substance melting at 104°C 4th endothermic peak at 131°C, melting temperature 130°C melting enthalpy 52 J/g

Example 4

Ethyl (S)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate

0.79 g (1.65 mMol) of ethyl (Z)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl)-aminocarbonyl-methyl]-benzoate, melting point 124-127°C, are dissolved in 10 ml of degassed solvent mixture (methanol/methylene chloride = 5/1) under an Argon atmosphere and added to a solution of 17 mg of the NOYORI-catalyst Ru(O-

acetyl)$_2$[(S)-BINAP] (prepared from [Ru(COD)Cl_2]$_n$ with (S)-BINAP [= (S)-2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl], triethylamine and sodium acetate) and 3 mg of titanium tetraisopropoxide in 10 ml of degassed solvent mixture (methanol/methylene chloride = 5/1). The reaction mixture is drawn into an autoclave evacuated at 10^{-2} mbar. This is flushed five times with hydrogen at 5 bar and finally hydrogenated at 30°C and 100 bar until the hydrogen uptake has ceased (154 hours). The reddish-brown solution is evaporated down in vacuo, the evaporation residue is dissolved in 80 ml of ether, filtered off from the undissolved brown flakes by means of activated charcoal and the resulting clear, bright yellow filtrate is evaporated down in vacuo. The evaporation residue (0.60 g) is refluxed in 60 ml of n-hexane and filtered hot to separate it from the insoluble matter. The filtrate is left to stand overnight at ambient temperature. The crystals which are precipitated are filtered off.
Yield: 0.45 g (56.7% of theory),
Melting point: 131-133°C (after sintering from 120°C)
Enantiomeric purity: ee = 39% (S) [HPLC method: see Example 1].

Example 5

Ethyl (S)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate

0.05 g (1.15 mMol) of 55% sodium hydride in oil are added to a solution of 0.68 g (1.15 mMol) of ethyl (S)-2-hydroxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate [melting point: 125-126°C; $[\alpha]_D^{20} = + 12.87°$ (c = 1.01 in methanol)] in 5 ml of anhydrous dimethylformamide and the mixture is stirred for 0.5 hours at ambient temperature. Then a solution of 0.12 ml (1.15 mMol) of ethyliodide in 2.5 ml

of anhydrous dimethylformamide is added dropwise thereto and the mixture is stirred for 5 hours at ambient temperature. It is evaporated down _in vacuo_, the residue is distributed between dilute sodium hydroxide solution and chloroform, the organic extract is dried, filtered and evaporated down _in vacuo_. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 10/1).

Yield: 0.48 g (67% of theory),

Melting point: 110-112°C

Calculated:	C 72.47	H 8.39	N 5.83
Found:	72.61	8.54	5.97

Enantiomeric purity: ee = 98.5% (S) [HPLC method: see Example 1].

Example 6

Ethyl (S)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from (S)-2-hydroxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid analogously to Example 5 using 2 equivalents of sodium hydride and 2 equivalents of ethyl iodide.

Yield: 42% of theory,

Melting point: 110-112°C

Calculated:	C 72.47	H 8.39	N 5.83
Found:	72.61	8.54	5.99

Enantiomeric purity: ee = 98.3% (S) [HPLC method: see Example 1].

Example 7

Ethyl (S)(+)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate and Ethyl (R)(-)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate

920 mg of ethyl (±)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate are separated, in single doses of 10 mg, on a preparative chiral phase HPLC column made by Baker, in which (S)-N-3,5-dinitrobenzoyl-leucine is covalently bonded to aminopropyl-silica gel (particle size: 40 μm; column length: 250 mm with an internal diameter of 20 mm; eluant: n-hexane/tetrahydrofuran/ethanol/methylene chloride (180/20/3/2); flow rate: 21.25 ml per minute; temperature: 27°C; UV-detection at 285 nm), in which first the (R)(-)-enantiomer (peak 1) and then the (S)(+)-enantiomer (peak 2) is eluted. After evaporation *in vacuo*, the following are obtained from the correspondingly cut and collected fractions:

Peak 1 fraction (R): 423 mg (crude),
Peak 2 fraction (S): 325 mg (crude).

In order to remove any impurities (including the stabiliser 2,6-di-tert.butyl-4-methyl-phenol contained in the tetrahydrofuran) the two fractions are each purified by column chromatography on silica gel (toluene/acetone = 10/1).

(R)(-)-enantiomer:

Yield: 234.5 mg (51% of theory),
Melting point: 122-124°C (petroleum ether + acetone)

Calculated:	C 72.47	H 8.39	N 5.83
Found:	72.40	8.18	5.71

$[\alpha]_D^{20} = -8.3°$ (c = 1 in methanol)

(S)-enantiomer:

Yield: 131.2 mg (28.5% of theory),

Melting point: 122-124°C (petroleum ether/acetone = 8/1)

Calculated:	C 72.47	H 8.39	N 5.83
Found:	72.28	8.44	5.70

$[\alpha]_D^{20}$ = + 8.3° (c = 1 in methanol)

A chiral cell OD column made by Daicel is also suitable for separating the enantiomers. The (R)-enantiomer is eluted after 6.8 minutes and the (S)-enantiomer after 8.5 minutes on a column 250 mm long with an internal diameter of 4.6 mm (eluant: absolute ethanol/(n-hexane + 0.2% diethylamine) = 5/95; temperature: 40°C; UV-detection at 245 nm).

Example 8

(R)(-)-2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid x 0.4 H_2O

Prepared from 150 mg (0.312 mMol) of ethyl (R)(-)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonyl-methyl]-benzoate [melting point: 122-124°C;
$[\alpha]_D^{20}$ = - 8.3° (c = 1 in methanol)] by saponification with 1N sodium hydroxide solution in ethanol analogously to Example 3.

Yield: 95.8 mg (66.7% of theory),

Melting point: 103-105°C (toluene/petroleum ether)

Calc. (x 0.4 H_2O):	C 70.51	H 8.01	N 6.09
Found:	70.88	7.79	5.81

Molecular peak M^+: Calculated: 452
Found: 452

$[\alpha]_D^{20}$ = - 6.5° (c = 1 in methanol)

Enantiomeric purity: ee = 99.7% (R) [HPLC method: see Example 3].

Example 9

(S)(+)-2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid x 0.4 H_2O

Prepared from 89 mg (0.198 mMol) of ethyl (S)(+)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate [melting point: 122-124°C; $[\alpha]_D^{20}$ = + 8.3° (c = 1 in methanol)] by saponification with 1N sodium hydroxide solution in ethanol analogously to Example 3.

Yield: 44.5 mg (48.8% of theory),

Melting point: 102-103°C (toluene/petroleum ether)

Calc.: (x 0.4 H_2O)	C 70.51	H 8.01
Found:	70.80	8.06

$[\alpha]_D^{20}$ = + 6.7° (c = 1 in methanol)

Enantiomeric purity: ee = 99.6% (S) [HPLC method: see Example 3].

Example 10

(S)-2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid

0.26 g (0.47 mMol) of benzyl (S)-2-ethoxy-4-[N-(1-(2-pipieridino-phenyl)-3-methyl-1-butyl)-aminocarbonyl-methyl]-benzoate (melting point: 91-92°C; $[\alpha]_D^{20}$ = + 9.5°; c = 1.05 in methanol) are hydrogenated in 10 ml of ethanol using 0.12 g of (10%) palladium/charcoal at 50°C and 5 bar of hydrogen. After 5 hours the catalyst is filtered off over kieselguhr and evaporated down *in vacuo*. The evaporation residue is crystallised from ethanol/water (2/1).

Yield: 0.15 g (70% of theory),

Melting point: 130-131°C

Calculated: C 71.64 H 8.02 N 6.19

Found: 71.76 8.12 6.05

Enantiomeric purity: ee = 99.6% [HPLC method: see Example 3].

Example 11

(S)-2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid

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102 mg (0.20 mMol) of tert.butyl (S)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate (melting point: 122-123°C; $[\alpha]_D^{20}$ = + 8.7°; c = 1 in methanol) are refluxed in 5 ml of benzene together with a few crystals of p-toluenesulphonic acid hydrate, for half a day. The desired product is then obtained, according to thin layer chromatography, according to the R_f value and mass spectrum.

Melting point: 129-131°C

Molecular peak M^+: Calc.: 452

Found: 452

Example 12

(S)-2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid

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200 mg (0.395 mMol) of tert.butyl (S)-2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate (melting point: 122-123°C; $[\alpha]_D^{20}$ = + 8.7°; c = 1 in methanol) are stirred into 2 ml of methylene chloride together with 0.45 g (3.95 mMol) of trifluoroacetic acid overnight at ambient temperature. The mixture is evaporated down *in vacuo* and the evaporation residue is distributed between aqueous sodium hydrogen carbonate solution and ethyl

acetate. The organic extract is dried, filtered and evaporated down *in vacuo*. The evaporation residue is crystallised from ethanol/water (2/1).

Yield: 115 mg (64.7% of theory),

Melting point: 126-128°C

Calculated:	C 71.64	H 8.02	N 6.19
Found:	71.39	7.91	6.06

$[\alpha]_D^{20} = + 6.97°$ (c = 0.975 in methanol)

Enantiomeric purity: ee = 99.8% [HPLC method: see Example 3].

Example 13

Tablets containing 0.25 mg AG-EE 623 ZW

One tablet contains:

0.250 mg of active substance
0.125 mg of N-methylglucamine
0.038 mg of polyvinylpyrrolidone
0.075 mg of polyoxyethylenepolyoxypropylene polymer
0.150 mg of microcrystalline cellulose

Preparation:

The active substance and excipients are dissolved in water at 90°C or the microcrystalline cellulose is suspended and the dispersion is evaporated down *in vacuo*. The dry mass is screened to a mesh size of 1 mm.

The following ingredients are added to the granulated active substance, for each tablet:

24.862 mg of sodium carboxymethyl starch
24.000 mg of microcrystalline cellulose
0.500 mg of magnesium stearate
50.000 mg

Round, biplanar tablets weighing 50 mg and measuring 5 mm in diameter are compressed from this mixture.

Example 14

Tablets containing 0.5 mg of AG-EE 623 ZW

One tablet contains:

0.500 mg of active substance
0.250 mg of N-methylglucamine
0.075 mg of polyvinylpyrrolidone
0.150 mg of polyoxyethylenepolyoxypropylene polymer
0.300 mg of microcrystalline cellulose

Preparation:

The active substance and excipients are dissolved in water at 90°C and the microcrystalline cellulose is suspended therein and the dispersion is evaporated down *in vacuo*. The dry mass is screened to a mesh size of 1 mm.

The following ingredients are added to the active substance granules for each tablet:

24.225 mg of sodium carboxymethyl starch
24.000 mg of microcrystalline cellulose
0.500 mg of magnesium stearate
50.000 mg

Round, biplanar tablets weighing 50 mg and measuring 5 mm in diameter are compressed from this mixture.

Example 15

Tablets containing 1.0 mg of AG-EE 623 ZW

One tablet contains:

1.00 mg of active substance
0.50 mg of N-methylglucamine
0.15 mg of polyvinylpyrrolidone
0.03 mg of polyoxyethylenepolyoxypropylene polymer
0.60 mg of microcrystalline cellulose

Preparation:

The active substance and excipients are dissolved in water at 90°C and the microcrystalline cellulose is suspended therein and the dispersion is evaporated down *in vacuo*. The dry mass is screened to a mesh size of 1 mm.

The following ingredients are added to the granulated active substance for each tablet:

23.22 mg of sodium carboxymethyl starch
24.00 mg of microcrystalline cellulose
0.50 mg of magnesium stearate
50.00 mg

Round, biplanar tablets weighing 50 mg and measuring 5 mm in diameter are compressed from this mixture.

Example 16

Tablets containing 1.5 mg of AG-EE 623 ZW

One tablet contains:

1.500 mg of active substance

0.750 mg of N-methylglucamine
0.225 mg of polyvinylpyrrolidone
0.045 mg of polyoxyethylenepolyoxypropylene polymer
0.900 mg of microcrystalline cellulose

Preparation:

The active substance and excipients are dissolved in water at 90°C and the microcrystalline cellulose is suspended therein and the dispersion is evaporated down *in vacuo*. The dry mass is screened to a mesh size of 1 mm.

The following ingredients are added to the granulated active substance for each tablet:

23.080 mg of sodium carboxymethyl starch
23.000 mg of microcrystalline cellulose
0.500 mg of magnesium stearate
50.000 mg

Round, biplanar tablets weighing 50 mg and measuring 5 mm in diameter are compressed from this mixture.

Example 17

Tablets containing 2.0 mg of AG-EE 623 ZW

One tablet contains:

2.00 mg of active substance
1.00 mg of L-lysine
1.00 mg of polyvinylpyrrolidone
1.00 mg of polyoxyethylenepolyoxypropylene polymer
4.00 mg of microcrystalline cellulose

Preparation:

The ingredients are dissolved in water at 90°C and the microcrystalline cellulose is suspended therein and the dispersion is processed in a spray dryer. The following ingredients are then added for each tablet:

20.35 mg of microcrystalline cellulose
20.00 mg of sodium carboxymethyl starch
0.65 mg of magnesium stearate
50.00 mg

Round, biconvex tablets weighing 50 mg and measuring 5 mm in diameter are compressed from this mixture and are given a flavour-masking coating of hydroxypropylmethylcellulose.

Example 18

Tablets containing 2.5 mg of AG-EE 623 ZW

One tablet contains:

2.50 mg of active substance
1.25 mg of L-lysine
1.25 mg of polyvinylpyrrolidone
1.25 mg of polyoxyethylenepolyoxypropylene polymer
4.10 mg of microcrystalline cellulose

Preparation:

The ingredients are dissolved in water at 90°C and the microcrystalline cellulose is suspended therein and the dispersion is processed in a spray dryer. Then the following ingredients are added for each tablet:

19.50 mg of microcrystalline cellulose
19.50 mg of sodium carboxymethyl starch
0.65 mg of magnesium stearate
50.00 mg

Round, biconvex tablets weighing 50 mg and measuring 5 mm in diameter are compressed from this mixture and given a flavour-masking coating of hydroxypropylmethyl cellulose.

Example 19

Tablets containing 3.0 mg of AG-EE 623 ZW

One tablet contains:

3.0 mg of active substance
1.5 mg of L-lysine
1.5 mg of polyvinylpyrrolidone
1.5 mg of polyoxyethylenepolyoxypropylene polymer

Preparation:

The ingredients are dissolved in water at 90°C and the solution is processed in a spray dryer. Then, for each tablet, the following ingredients are added:

21.5 mg of microcrystalline cellulose
21.0 mg of sodium carboxymethyl starch
50.0 mg

Round, biconvex tablets weighing 50 mg and measuring 5 mm in diameter are compressed from this mixture and given a flavour-masking coating of hydroxypropylmethyl cellulose.

Example 20

Tablets containing 5 mg of AG-EE 623 ZW

One tablet contains:

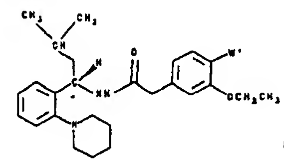
5.0 mg of active substance
2.5 mg of L-lysine
2.5 mg of polyvinylpyrrolidone
2.5 mg of polyoxyethylenepolyoxypropylene polymer

Preparation:

The ingredients are dissolved in water at 90°C and the solution is processed in a spray dryer. Then, for each tablet, the following ingredients are added:

19.0 mg of microcrystalline cellulose
18.5 mg of sodium carboxymethyl starch
50.0 mg

Round, biconvex tablets weighing 50 mg and measuring 5 mm in diameter are compressed from this mixture and given a flavour-masking coating of hydroxypropylmethyl cellulose.



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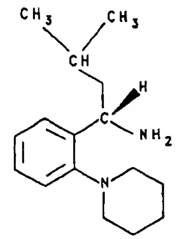

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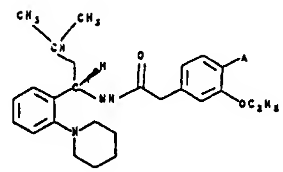

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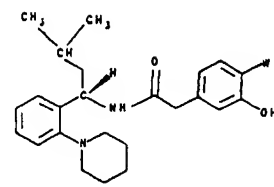

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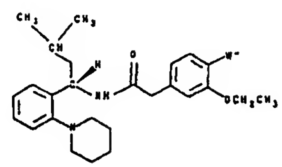

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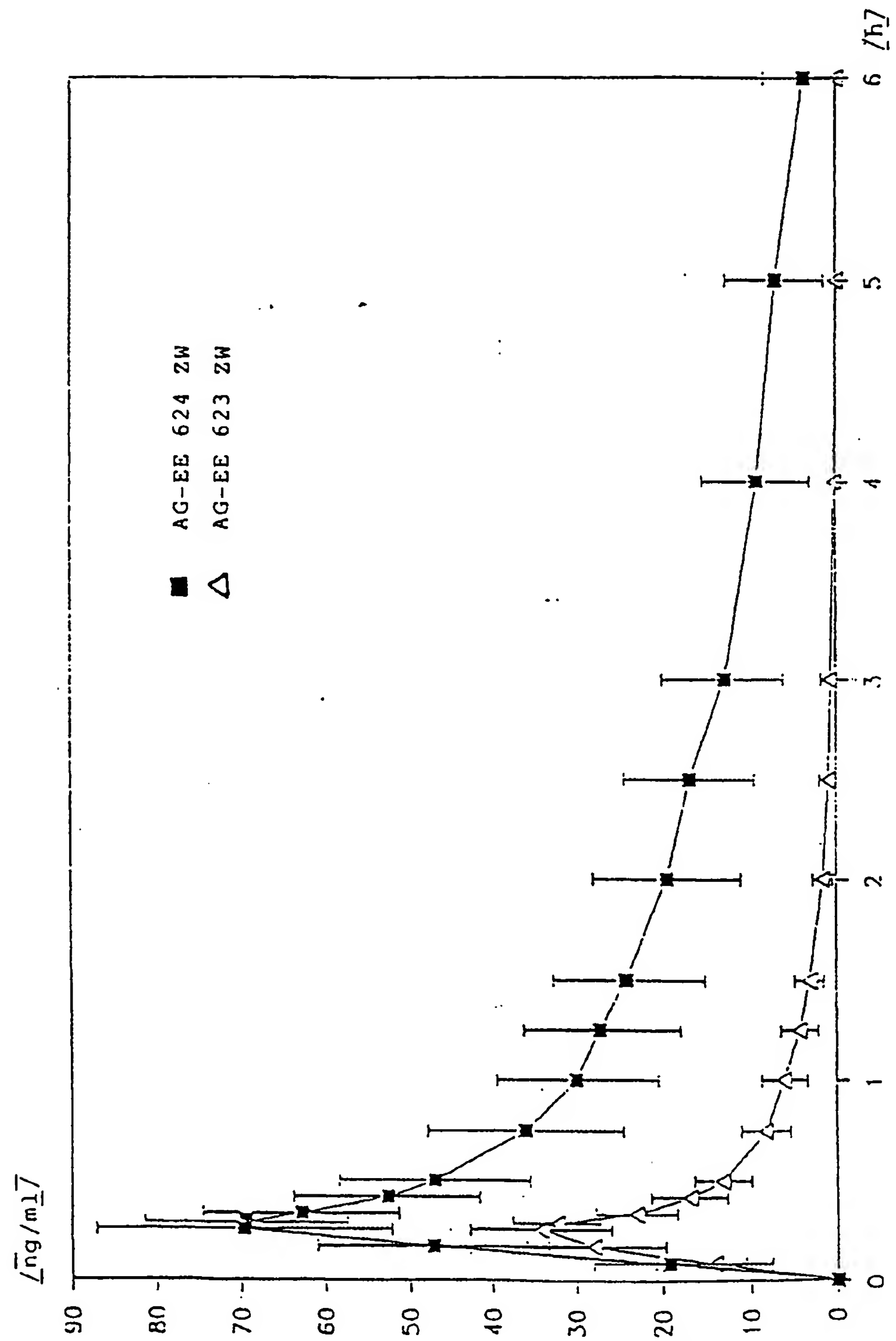
Figure 1



Patent Agents
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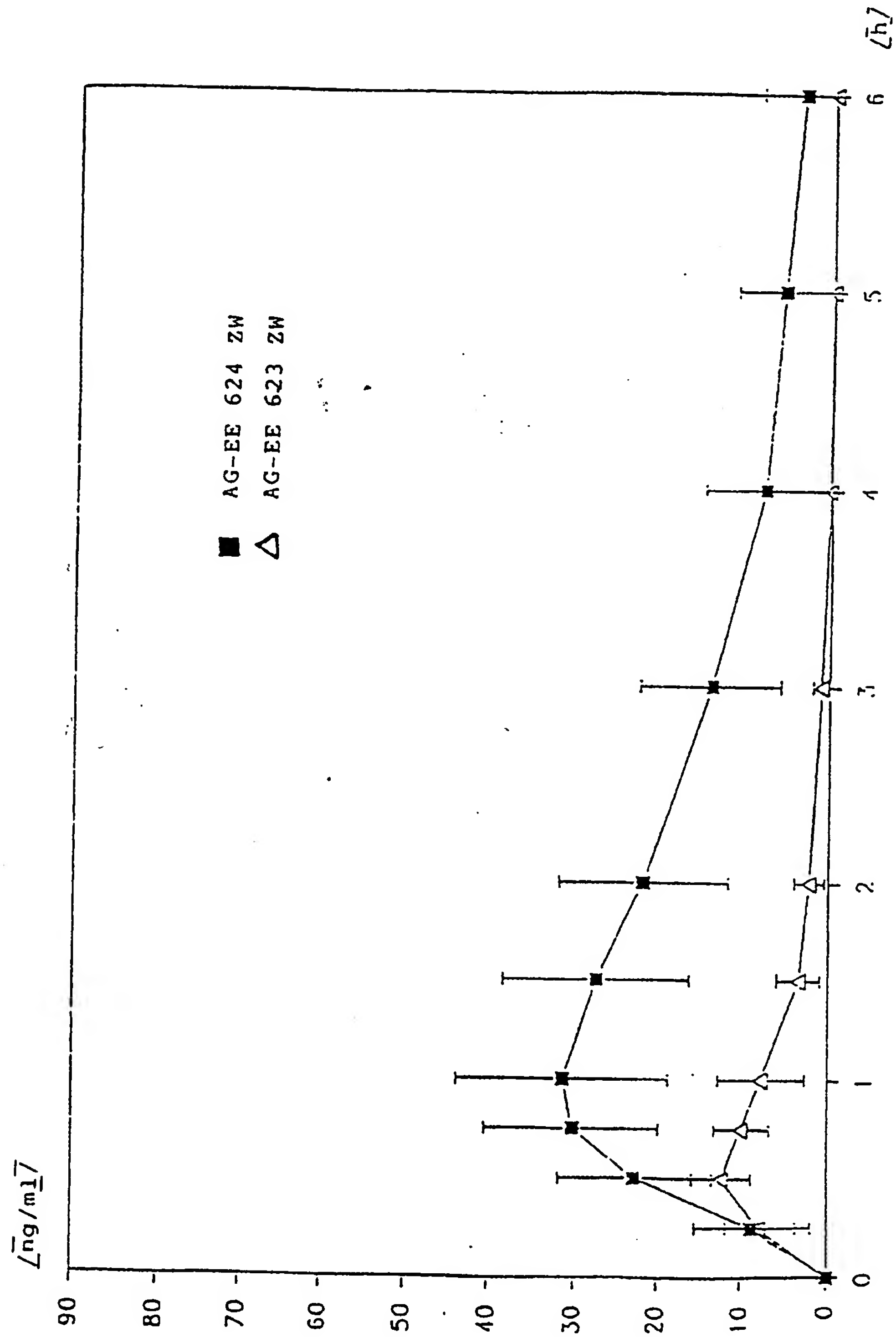
Figure 2



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